

## **STILBŒSTROL (DIETHYLSTILBESTROL) AND THE RISK OF OVARIAN CANCER**

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**Summary** A follow-up survey of 908 women who had received 'Premarin' (conjugated equine œstrogen) for menopausal symptoms revealed 8 cases of ovarian cancer. This risk was 2 to 3 times greater than expected. The risk increased with the strength of premarin tablet usually taken, but not with the duration of use or total dose ingested. The excess risk of ovarian cancer in this group occurred primarily among 21 women who had also used stilbœstrol (diethylstilbestrol). The results of this small trial are consistent with the increasing incidence of ovarian cancer in post-menopausal women in the U.S.A., and with the occurrence of stilbœstrol-induced ovarian neoplasms in dogs.

### **INTRODUCTION**

LITTLE is known about possible causes of ovarian cancer. Since there are over 10 000 deaths from this highly fatal tumour each year in the U.S.,<sup>1</sup> any reasonable clue to a preventable cause should be investigated. A follow-up study of a large group of œstrogen-treated women has pointed to a possible risk factor for this cancer.

### **METHODS**

We reviewed the record of every woman seen in one private practice of gynaecology in Louisville, Kentucky, since 1939. Since most patients were White, the study was limited to all White women treated orally with 'Premarin' (conjugated equine œstrogen) for at least six months. The initial medical history was abstracted, as was a detailed record of hormone treatment and a record of each woman's continuing health.

Attempts were made to follow all women through the end of 1969, and to obtain information on the occurrence of malignancy, cause of death if dead, and use of hormonal preparations outside of this gynaecology practice.

Expected numbers of new cases of cancer in the study group were calculated by applying the age and time specific incidence-rates for women in the general population to the corresponding person-years accrued by the study group. Rates for the U.S. general population were derived from the Connecticut tumour registry,<sup>2-4</sup> all areas in the Second and Third National Cancer Surveys, and southern areas of the National Surveys.<sup>5-6</sup> Five-year age and time intervals were used in all 3 sets of popula-

tion rates. For the National Cancer Surveys, rates for White females from the Second Survey (1947) were used for 1940-44 and 1945-49 while interpolations with the Third Survey (1969-71) were used to calculate rates between 1950 and 1969.

Expected numbers of ovarian cancers were estimated for the 908 women who had at least one ovary when first becoming eligible for the study. Furthermore, for those women undergoing an oophorectomy during the follow-up, only those person-years accrued before the procedure were included for the calculation of an expected value.

The measure of strength of association used is the ratio of an observed to an expected number of cases, referred to as the relative risk (R.R.). Exact 95% confidence intervals (C.I.) were calculated for this ratio under the assumption that the observed number is a variable with Poisson distribution. When the C.I. for the ratio does not include 1.0 (no association) then the R.R. is statistically significant at the  $P < 0.05$  level.

#### RESULTS

8 ovarian cancers and 1 cancer of the fallopian tube were observed during the follow-up. 3.4 cancers of the ovary, fallopian tube, and broad ligament (I.C.D. 163) would have been expected based on the rates from all areas in the National Cancer Surveys (R.R.=2.6, 95% C.I.=1.2-5.0). Since 98% of neoplasms coded I.C.D. 163 are primary cancers of the ovary, all subsequent analyses were limited to the 8 ovarian cancers, and the expected values decreased by 2%. The R.R. for ovarian cancer ranged from 2.4 to 2.7, based on the three sets of rates used to generate the expected values (table 1). These R.R.s were statistically significant at the 5% level. Expected values for all subsequent analyses were based on the rates from all areas in the National Cancer Surveys.

TABLE 1—EXPECTED INCIDENCE OF CANCERS OF THE OVARY, RELATIVE RISKS (COMPARED TO 8 CASES OBSERVED), AND 95% CONFIDENCE INTERVALS ACCORDING TO POPULATION-RATES USED TO GENERATE EXPECTED VALUES

| Population-rates           | Expected no. | Relative risk | 95% confidence intervals |
|----------------------------|--------------|---------------|--------------------------|
| National Survey, all areas | 3.3          | 2.4           | 1.0-4.8                  |
| National Survey, south     | 3.2          | 2.5           | 1.1-4.9                  |
| Connecticut                | 3.0          | 2.7           | 1.1-5.3                  |

No appreciable trends in excess risk were noted with respect to age at first premarin use or interval between first use and tumour diagnosis. Estimates of R.R. were made for three measures of dose of premarin (table II). The R.R. rose with increasing strength of the tablet usually used, but not with the duration of use or total accumulated dose.

The excess risk of ovarian cancer was restricted to the group of 99 women who had also taken "other oestrogens". 4 ovarian cancers occurred in this group in

TABLE II—OBSERVED AND EXPECTED INCIDENCE OF CANCERS OF THE OVARY, RELATIVE RISKS, AND 95% CONFIDENCE INTERVALS BY STRENGTH OF PREMARIN TABLET USUALLY USED, TOTAL YEARS OF USE, AND TOTAL ACCUMULATED DOSE

|                             | Observed | Expected | Relative risk | 95% confidence intervals |
|-----------------------------|----------|----------|---------------|--------------------------|
| <i>Usual strength (mg):</i> |          |          |               |                          |
| 0.3                         | 3        | 1.8      | 1.7           | 0.3- 4.9                 |
| 0.625                       | 3        | 1.2      | 2.5           | 0.5- 7.3                 |
| >1.25                       | 2        | 0.3      | 6.7           | 0.8-24.1                 |
| <i>Years of use:</i>        |          |          |               |                          |
| ≤5                          | 6        | 2.1      | 2.9           | 1.0- 6.2                 |
| >5                          | 2        | 1.1      | 1.8           | 0.2- 6.6                 |
| <i>Total dose (mg):</i>     |          |          |               |                          |
| ≤800                        | 6        | 2.2      | 2.7           | 1.0- 5.9                 |
| >800                        | 2        | 1.0      | 2.0           | 0.2- 7.2                 |

which 0.5 cases were expected (R.R.=8.0, 95% C.I.=2.2-20.5). The R.R. among those taking only premarin was 1.4 (95% C.I.=0.4-3.7)—i.e., 4 observed cases and an expected value of 2.8. The "other oestrogens" taken by the 99 women consisted mainly of conjugated oestrogens identical or quite similar to premarin. However, 3 of the 4 patients with ovarian cancer using other oestrogens had taken stilboestrol for a period of 1 year or more. The expected value in the 21 patients in this series who had taken stilboestrol in addition to premarin was 0.1 (R.R.=30, 95% C.I.=6.2-87.7). The 3 tumours occurred twelve to nineteen years after the use of the drug.

#### DISCUSSION

The excess of ovarian cancer among women receiving oestrogens for menopausal symptoms, primarily stilboestrol preparations, is based on small numbers and may be due to chance. However, the finding is consistent with observations in laboratory animals. The earliest report, in 1959, concerned 8 female dogs treated with stilboestrol.<sup>7</sup> Within nineteen months, ovarian carcinoma had developed in 6 dogs: 1 had an adenoma and 1 showed ovarian hyperplasia. In a subsequent study, 13 bitches were given various doses of stilboestrol; 3 also received progesterone.<sup>8</sup> In 12 invasive ovarian neoplasms developed, with metastases in 9. The remaining dog had a peculiar papillary "dysplasia" of the ovary without evidence of local invasion, but with extensive metastases. The cancers developing in this experiment were not related to age, breed, or concurrent progesterone treatment. They were hormone-dependent, since stilboestrol withdrawal was followed in several months by their regression. Similar results were subsequently described in dogs given a chemically related synthetic oestrogen (trans-4,4<sup>1</sup> dimethyl- $\alpha$ , $\alpha$ <sup>1</sup> diethylstilbene).<sup>9</sup>

While stilboestrol is not the most common agent for treating menopausal symptoms, it has been used many years for this purpose, and is now prescribed for as many as 41 000 women in the U.S.<sup>10</sup> If there were a large excess risk of ovarian cancer associated with the use of this drug, one would expect the incidence of ovarian cancer among postmenopausal women to be increasing. In fact, U.S. mortality trends indicate a steady climb in the rates of ovarian cancer among older women (age 60+), compared to relatively constant or declining rates in younger women.<sup>11,12</sup> Similar trends are present in the incidence data from the two National Cancer Surveys.<sup>5-6</sup> Thus, the excess of ovarian cancer among women using stilboestrol for menopausal symptoms in our study is consistent with the results of animal experiments and with time trend analyses, and indicates the need for further long-term studies to evaluate the risk of ovarian cancer associated with oestrogenic compounds.

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